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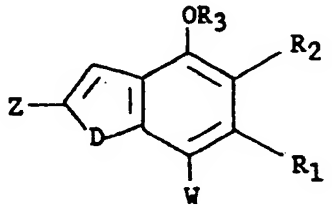

(I)

(57) Abstract

The present invention provides certain novel 1,4-dihydrothionapthoquinone and heterocyclic cogeners of Formula (I), which are useful as inhibitors of leukotriene biosynthesis and as inhibitors of lipoxygenase. They are thus employed wherever it is medically necessary or desirable to inhibit these systems.

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1,4-DIHYDROTHIONAPTHOQUINONE AND HETEROCYCLIC CONGENERS WHICH INHIBIT LIPOXYGENASE ENZYMES

BACKGROUND OF THE INVENTION

The present invention provides novel 1,4-dihydrothionatpthoquinone and heterocyclic congeners which are useful as inhibitors of the synthesis of leukotrienes and as inhibitors of the action of lipoxygenase in mammalian metabolism.

The leukotrienes are a class of unsaturated fatty acid compounds which are derived from arachidonic acid by the action of lipoxygenase. See, e.g., Samuelsson, Trends in Pharmacological Sciences, 5:227 (1980); and Samuelsson, et al., Annu. Rev. Biochem. 47:997-1029 (1978). For a discussion of leukotriene nomenclature, see Samuelsson, et al., Prostaglandins, 19:645 (1980).

The leukotrienes have been discovered as potent constrictors of human bronchi. That is, certain leukotrienes are mediators of the action of slow-reacting substance of anaphylaxis (SRS-A). See, e.g., Dahlén, Nature, 288:484 (1980). These compounds are therefore important mediators of bronchoconstriction in humans.

The role of leukotrienes as agonists in immediate hypersensitivity and other pathological conditions has led to research into inhibitors of leukotriene biosynthesis and leukotriene antagonists. See, e.g., Corey, et al., Tetrahedron Letters 21:4243 (1980).

Mucus secreted from submucosal glands and surface at the epithelial cells combines with water to form part of the respiratory tract secretions. In healthy states mucous secretions in the respiratory tract is normal being about 50 to 150 ml per day in man. The excessive production of mucus, however, is an important feature of many pulmonary diseases. For example, in chronic bronchitis the flow of mucus increases up to four times. The lack of the ability of the patient to deal with this hyper-production leads to paths of physiological conditions of the airways such as chronic bronchitis, asthma, and cystic fibrosis where there is a defect in consistency in clearance of the mucus. Therefore it is medically desirable to regulate the hypersecretion of mucus (J.G. Widdicobe, British Medical Bulletin, 34:57 (1978)). Historically, attempts have been made to treat the symptoms without regulation of the root cause. For example, mucolytics, acetylcysteine containing solutions, as well as iodides have been used. Also, antibiotics are used to treat infec-

tions in cystic fibrosis because no known drug can regulate the consistency of the mucus in this disease condition.

Leukotrienes, particularly leukotriene C_4 (LTC_4) and leukotriene D_4 (LTD_4) have been shown to be potent mucous secretagogues. Both LTC_4 and LTD_4 increase the release of mucus from human airways in vitro. Z. Maron, et al., Am. Rev. Respir. Dis. 126, 449-451 (1982); S.J. Coles, et al., Prostaglandins 25, 155-170 (1983) and from canine tracheas in vivo. H.G. Johnson, et al., International Jr. Immunopharmacol. 5, 178 (1983); H.G. Johnson, et al., Prostaglandins 25, 237-243 (1983). Arachidonic acid, metabolic products of arachidonic acid, monohydroxy-eicosatetraenoic acid, and prostaglandins also release mucus from human airway. Z. Marom, et al., Jr. Clinical Investigations, 67, 1695-1702 (1981).

LTC_4 was effective in stimulating mucus release in vivo in the cat but not in vitro on cat trachea tissue. A.C. Peatfield, et al., British Journal of Pharmacology, 77, 391-393 (1982). J.H. Shelhamer, et al., Chest 81, 36S (1982) summarizes the nature of evidence available suggesting that lipoxygenase products generated by the airways in vitro might be responsible for the augmented mucus release.

O. Cromwell, et al., The Lancet, July 25, 1981, pp. 164-165, identified LTB_4 and LTD_4 in the sputum of cystic fibrosis patients and speculated, therefore, that inhibitors of the lipoxygenase pathway might be capable of reversing the airway obstruction in such patients.

T. Ahmed, et al., Am. Rev. Respir. Dis. 124, 110-114 (1981) demonstrated that FPL 55712, an LTC_4 antagonist when given prior to antigen challenge was effective in reversing the tracheal mucus velocity in patients with a history of bronchial asthma but concluded that the clinical significance of FPL 55712 remains to be demonstrated.

In mammalian metabolism, arachidonic acid is transformed to 12-L- hydroperoxy-5,8,10,14-eicosatetraenoic acid by the action of 12-lipoxygenase. See, Hamberg, et al., Proceedings of the National Academy of Science, 71:3400-3404 (1974). Similarly, 5-lipoxygenase transforms arachidonic acid into 5-S-hydroperoxy-6,8,11,14-eicosatetraenoic acid. Thus, an agent which inhibits the action of lipoxygenase would be useful in treating or preventing untoward conditions associated with lipoxygenase products.

Just as the actions of the 5-lipoxygenase enzymes lead to leukotrienes of the B_4, C_4, D_4 and E_4 series, the 15-lipoxygenase reaction, using for example arachidonic acid as substitute, provides 15-hydroperoxyeicosatetiaenoic acid (15-HPETE) which can be converted to $14,15\text{-LTA}_4$ as reduced to 15-hydroxyeicosatetraenoic acid, (T. Schewe, S.M. Rapoport, H. Kuhn, Adv. Enzymol. 58, 191 (1986). Both the human epithilial cell and trachea produce large amounts of 15-HETE and its metabolites, (D. Henke, M.R. Knowles, R. Boucher, T. Eling, Ann. Rev. Respir. Dis., 135, A508 (1987); J.A. Hunter, W.E. Finkheiner, J.A. Nadel, E.J. Goetzl, M.J. Holtzman, Clin. Res., 33, 78A (1985); Proc. Natl. Acad. Sci. (USA), 82, 4633 (1985)). Antigen challenge of asthmatic patients produced marked increases of 15-HETE in the fluid obtained by bronchoalveolar lavage. (J.J. Murray, A.B. Tonnel, A.R. Brash, L.J. Roberts, II, P. Gosset, R. Workman, A. Capron, J.A. Oates, New England Journal of Medicine, 315, 800 (1986). The pathophysiology of administered 15-HETE include profound increases in mucus production and increases in filtration of polymorphonuclear (PMN) leukocyte cell infiltration into lung tissue (H.G. Johnson, M.L. McNee, F.F. Sun, Am. Rev. Resp. Dis., 131, 917 (1985)).

It can be concluded that compounds which inhibit the formation of 15-HETE type products by interfacing with their biosynthesis would provide a method for the prophylactic or therapeutic treatment of allergy of a reagin or non-reagin indicated nature. Asthma is preferentially treated by compounds of this invention but any allergy wherein LTB_4, LTC_4, LTD_4, LTE_4, and/or 15-HETE-type products are thought to be involved as anaphylaxis indicators can be treated.

Therefore, compounds which inhibit the action of lipoxygenase are useful in the treatment of inflammatory conditions where it is desirable to prevent migration of polymorphonuclear leukocytes to the inflammatory site. They are also useful in the treatment of asthma.

PRIOR ART

Certain substituted napththalenes, indoles, benzofurans and benzothiophenes are disclosed as lipoxygenase inhibitors in commonly assigned U.S. Patent 4,737,519.

Certain chromium complexes of benzofurans and benzothiophenes are disclosed in K.H. Dotz, et al., Chem. Ber. 111:2517 (1978).

Certain napththaquinones are disclosed as intermediates for the preparation of Vitamin K-type derivatives in U.S. patents 4,374,775

and 4,320,065. U.S. patents 4,358,461; 4,388,312; and 4,393,075 disclose certain naphthaquinones as SRS-A and lipoxygenase inhibitors. Intermediates for these latter compounds are disclosed in U.S. patent 4,199,531. W.D. Wulff, et al., have described the use of Fischer carbene complexes in the preparation of certain hydroquinone mono ethers in Abstracts 88 and 89 from the Fall 1983 American Chemical Society Meeting in Washington D.C. (August 18-19, 1983).

A number of substituted 1-hydroxy, 4-methoxy naphthalenes are known. Thus K.H. Dotz, et al., J. Organometal. Chem. 247(2):187-201 (1983) discloses 4-methoxy-1-naphthalenols substituted in the 2 and 3 positions by phenyl, substituted phenyl, methyl, ethyl, octyl, and propyl. 4-Methoxy-2-phenyl-1-naphthalenol is disclosed in K. Buggle, et al., Jr. Chem. Soc., Perkin Trans 1 (6):572-575 (1975). 4-Methoxy- 2.3-diphenyl-1-naphthalenol is disclosed in K.H. Dotz, J. Organmet. Chem. 140(2):177-86 (1977). 4-Methoxy-2,3-dimethyl-1-naphthalenol is disclosed in K.H. Dotz, et al., Chem. Ber. 110(4):1555-63 (1977). 2-Tert-butyl-4-methoxy-1-naphthol is disclosed in Japanese patent 7010339. U.S. patent 3,948,958 discloses 4-methoxy-3-methyl--1-naphthenol. 4-Methoxy-2-methyl-1-naphthenol is disclosed in I.D. Snyder, et al., Journal of the American Chemical Society, 96(26):-8046-53 (1974). The 2,3- unsubstituted 4-methoxy-1-naphthenol compound is also known. See, e.g., British patent 1,122,085.

Certain 1-acetoxy-4-methoxy-naphthalenes are also known. Thus, 4-methoxy-1-naphthalenol, acetate is disclosed in German OLS 2802666. The corresponding 2,3-dimethyl compound is disclosed in F.M. Dean, et al., J. Chem. Soc., Perkin Trans. 1(20):2289-94 (1977). 4-Methoxy-2-phenyl-1-naphthalenol is disclosed in O. Gonclalves de Lima, et al., Rev. Inst. Antibiot., Univ. Recife 5(1-2):3-9 (1963).

SUMMARY OF THE INVENTION

The present invention particularly provides:

a compound of the Formula I or a pharmacologically acceptable acid addition salt thereof wherein R_1 and R_2 are the same or different and are

(a) hydrogen,

(b) (C_1-C_{10})alkyl,

(c) (C_2-C_{10})alkenyl, or

(d) PhX;

wherein (PhX) is phenyl substituted by zero to 3 of the following:

(a) (C_1-C_4)alkyl,
(b) chloro,
(c) fluoro,
(d) bromo,
(e) nitro,
(f) trifluoromethyl; or
(g) OR_4;

wherein D is
(a) -CH=CH-,
(b) -N(CH_3),
(c) -S-, or
(d) -O-;

wherein R_3 is
(a) CH_3-C(0)-,
(b) hydrogen,
(c) -C(0)-($CR_{17}R_{18}$)$_m$-(CH_2)$_n$-$NR_{14}R_{15}$,
(d) -C(0)-AA, or
(e) -C(0)-PhX-NH_2;

wherein m is 1, 2, 3, or 4;

wherein n is 0, 1, 2, 3, 4, or 5;

wherein -C(0)AA is the acyl portion derived from any naturally occurring alpha-amino acid;

wherein R_{14} and R_{15} are the same or different and are:
(a) hydrogen,
(b) (C_1-C_{10}) alkyl,
(c) -C(0)R_{16},
(d) -C(0)-PhX, or
(e) -PhX;

with the proviso that R_{14} and R_{15} are other than hydrogen when n is zero;

wherein R_{16} is (C_1-C_4) alkyl;

wherein R_{17} and R_{18} are the same or different and are:
(a) hydrogen,
(b) (C_1-C_{10}) alkyl,
(c) -CH_2-PhX, or
(d) -PhX;

with the proviso that each occurrence of R_{17} and R_{18} is the same or different;

wherein PhX-NH_2 is an amino-substituted phenyl group additionally substituted by zero to 3 of the following:

(a) (C_1-C_4) alkyl,

(b) chloro,

(c) fluoro,

(d) bromo,

(e) nitro,

(f) trifluoromethyl, or

(g) OR_4;

wherein R_4 is

(a) hydrogen, or

(b) (C_1-C_4)alkyl;

wherein W is

(a) OCH_3 or

(b) $S(O)_qY$

wherein q is 0, 1 or 2;

wherein Y is

(a) (C_1-C_4)alkyl,

(b) (C_1-C_4) alkenyl,

(c) PhX;

wherein W is $S(O)_qY$ then Z is

(a) hydrogen or

(b) (C_1-C_4)alkyl;

wherein W is OCH_3 then Z is (C_1-C_4)alkyl.

Excluding those compounds where Z is hydrogen, D is ethylene and R_1 and R_3 are hydrogen, R_2 is phenyl, and W is SCH_3 or SPh; or where R_1 and R_2 are methyl, R_3 is hydrogen and W is SCH_3; or where R_1 is hydrogen, R_2 is phenyl, R_3 is $COCH_3$ and W is SCH_3.

A method for treating or preventing the hypersecretion of mucus in the respiratory tract of an allergic or asthmatic patient in need thereof which comprises administering a compound of Formula I to a patient in an amount effective to treat or prevent said hypersecretion of mucus. Excluding those compounds where D is O or -CH=CH-, R_3 is $COCH_3$, Z is hydrogen and R_1 and R_2 are both ethyl, phenyl or a phenyl and a methyl or an ethyl ester.

DETAILED DESCRIPTION OF THE INVENTION

The compounds of the present invention will be named herein using the Chemical Abstracts numbering system (see Naming and

Indexing of Chemical Substances for Chemical Abstracts during the Ninth Collective Period (1972-1976), a reprint of section IV from the Volume 76 Index Guide.) When D is -CH=CH-, the compounds are named as naphthalenes. When D is -N(CH_3), the compounds are named as N-methyl indoles, and when D is -O- and -S-, the compounds are named as benzofurans and benzothiophenes, respectively.

As noted, compounds of this invention are useful to inhibit the formation of slow reacting substance of anaphylaxis (SRS-A) and thus its smooth muscle contracting and secretory effects.

The carbon atom content of various hydrocarbon-containing moieties is indicated by a prefix designating the minimum and maximum number of carbon atoms in the moiety, i.e., the prefix (C_i-C_j) indicates a moiety of the integer "i" to the integer "j" carbon atoms, inclusive. Thus (C_1-C_3)alkyl refers to alkyl of one to 3 carbon atoms, inclusive, or methyl, ethyl, propyl, and isopropyl.

Examples of alkyl of one to 10 carbon atoms, inclusive, are methyl, ethyl, propyl, butyl, pentyl, hexyl, heptyl, octyl, nonyl, decyl, and isomeric forms thereof.

Examples of C_2-C_{10} alkenyl are allyl, 1-methylallyl, 2-methylallyl (methallyl), 2-butenyl (crotyl), 3-butenyl, 1,2-dimethylallyl, 1,1-dimethylallyl, 2-ethylallyl, 1-methyl-2-butenyl, 2-methyl-2-butenyl, 3-methyl-2-butenyl, 3-pentenyl, 2,3-dimethyl-2-butenyl, 1,1,2-trimethylallyl, 1,3-dimethyl-2-butenyl, 1-ethyl-2-butenyl, 4-methyl-2-pentenyl, 2-ethyl-2-pentenyl, 4,4-dimethyl-2-pentenyl, 2-heptenyl, 2-octenyl, 5-octenyl, 1,4-dimethyl-1-hexenyl, and the like.

Examples of PhX are phenyl, p-chlorophenyl, m-bromophenyl, 2,4-difluorophenyl, 2,4,6-trichlorophenyl, p-tolyl, m-tolyl, o-tolyl, p-ethylphenyl, p-tert-butylphenyl, 2,5-dimethylphenyl, 4-chloro-2-methylphenyl, 2,4-dichloro-3-methylphenyl, p-nitrophenyl, p-methoxyphenyl, 3-trifluorophenyl, and 4-hydroxyphenyl.

Examples of acids, which are commonly used for salt formation, are hydrochloric acid, hydrobromic acid, hydroiodic acid, methanesulfonic acid, ethanesulfonic acid, benzenesulfonic acid, phosphoric acid, acetic acid, propionate acid, succinic acid, para-toluenesulfonic acid, maleic acid, tartaric acid, and lactic acid.

By -C(O)-AA is meant the acyl part of an amino acid including the naturally-occurring acids such as: glycine, alanine, valine, leucine, isoleucine, phenylalanine, lysine, proline, tryptophan,

methionine, serine, threonine, cysteine, tyrosine, asparagine, glutamine, aspartic acid, glutamic acid, arginine, ornithine, and histidine, and synthetic derivatives thereof. These compounds may be in L or D configuration and are well known and readily available to those skilled in the art. Thus, AA-COOH would represent the amino acids themselves.

When R_3 is definitions (c), (d), or (e), the substituent is an amino acid derivative which may be in the "D" and/or "L" configuration, the prefixes "D" and "L" are a means of indicating the relative configurations of various optically active compounds, especially carbohydrates. The compound glyceraldehyde, $CH_2OHCHOHCHO$, was selected as a standard of reference, because it is the simplest carbohydrate - an aldotriose - capable of optical isomerism. (+)-Glyceraldehyde was arbitrarily assigned a configuration and was designated D-glyceraldehyde, and (-)-glyceraldehyde was assigned a second configuration and was designated L-glyceraldehyde. R. T. Morrison & R. N. Boyd, Organic Chemistry 1087-88 (1978). Compounds related configurationally to D-glyceraldehyde are given the designation D, and compounds related to L-glyceraldehyde are given the designation L. Organic Chemistry at 1089. In the present invention, both L and D configurations are observed; however, the L-configuration predominates and is preferred.

To demonstrate the SRS-A inhibitory activity of the compounds of this invention, compounds of this invention were evaluated in a standard laboratory test. This test is conducted in rat mononuclear cells incubated in the presence of cysteine and challenged with a calcium ionophore (which induces SRS-A formation). Among the non-amino compounds of this invention, in this test system, and are preferred. At a concentration of 10 micrograms/ml, these compounds inhibited the synthesis of SRS-A 100% and 95%, respectively.

The amino acyl compounds of this invention, when R_3 is $-C(O)-(CR_{17}R_{18})_m-(CH_2)_n-NR_{14}R_{15}$, -C(O)-AA or $-C(O)-PhX-NH_2$, are also preferred for drug formulation because they are more easily crystallizable (particularly, the salts) and are more water soluble. On the basis of biological activity and ease of formulation, hydrochloride is preferred.

Some of the novel compounds of this invention have been shown to be active as inhibitors of the production of 5-lipoxygenase derived

leukotrienes and some of the compounds of this invention have been shown to be active as inhibitors of the lipoxygenase enzyme system. Some of these compounds are effective in both systems. All of the compounds of this invention are active as inhibitors of at least one of these two systems. Accordingly, these novel compounds are useful for administration to mammals, including humans, whenever it is desirable medically to inhibit either of these systems. Inhibitors of either system are useful in the treatment of asthma.

Thus, all of the compounds of this invention are useful in the treatment of asthma. For example, these compounds are useful as bronchodilators or as inhibitors of mediators such as SRS-A which are released from cells activated by an antigen-antibody complex. Thus, these compounds control spasm and facilitate breathing in conditions such as bronchial asthma, bronchitis, bronchiectasis, pneumonia and emphysema. For these purposes, these compounds are administered in a variety of dosage forms, e.g., orally in the form of tablets, capsules, or liquids; rectally in the form of suppositories; parenterally, subcutaneously, or intramuscularly, with intravenous administration being preferred in emergency situations, by inhalation in the form of aerosols or solutions for nebulizers; or by insufflation in the form of powder. Doses in the range of about 0.01 to 50 mg per kg of body weight are used 1 to 4 times a day, the exact dose depending on the age, weight, and condition of the patient and on the frequency and route of administration. For the above use these compounds can be combined advantageously with other anti-asthmatic agents, such as sympathomimetics (isoproterenol, phenylephrine, ephedrine, etc.); xanthine derivatives (theophylline and aminophylline); and corticosteroids (ACTH and prednisolone).

As noted above, the compounds of this invention are particularly useful in treating asthma, but any allergy wherein slow reacting substance of anaphylaxis (SRSA) is thought to be involved as a pharmacological mediator of anaphylaxis can be treated. For example, the compounds can be used for treatment of such conditions as allergic rhinitis, food allergy and urticaria as well as asthma.

The compounds of this invention are effectively administered to human asthma patients by any covenient route such as oral inhalation, aerosol inhalation, parenterally, (orally, intravenously, interperitoneally), transdermally, topically and the like.

The amino acyl compounds of this invention are preferred for intravenous infusions and the like. Particularly preferred in this regard is L-Valine, 1-methylthio-3-n-butyl-4-naphalenyl ester, monohydrochloride. The non-acyl-amino compounds of this invention are preferred for topical administration.

For administration by the oral inhalation route with conventional nebulizers or by oxygen aerosolization it is convenient to provide the instant active ingredient in dilute solution, preferably at concentra-tions of about 1 part of medicament to form about 100 to 200 parts by weight of total solution. Entirely conventional additives may be employed to stabilize these solutions or to provide isotonic media, for example, sodium chloride, sodium citrate, citric acid, sodium bissulfite, and the like can be employed.

For administration as a self-propelled dosage unit for administering the active ingredient in aerosol form suitable for inhalation therapy the composition can comprise the active ingredient suspended in an inert propellant (such as a mixture of dichlorodifluoromethane and dichlorotetrafluoroethane) together with a co-solvent, such as ethanol, flavoring materials and stabilizers. Instead of a co-solvent there can also be used a dispensing agent such as oleyl alcohol. Suitable means to employ the aerosol inhalation therapy technique are described fully in U.S. Pat. No. 2,868,691 for example.

The lipoxygenase inhibitor compounds of this invention are useful whenever it is desired to inhibit platelet aggregation, reduce the adhesive character of platelets, and remove or prevent the formation of thrombi in mammals, including man, rabbits, dogs, and rats. For example, these compounds are useful in the prevention of myocardial infarcts, to prevent post-operative thrombosis, to promote patency of vascular grafts following surgery, and to treat conditions such as atherosclerosis, arteriosclerosis, blood clotting defects due to lipemia, and other clinical conditions. For these purposes, these compounds are administered systemically, e.g., intravenously, subcutaneously, intramuscularly, and in the form of sterile implants for prolonged action. For rapid response, especially in emergency situations, the intravenous route of administration is preferred. Doses in the range about 0.005 to about 20 mg per kg of body weight per day are used, the exact dose depending on the age, weight, and condition of the patient or animal, and on the frequency and route of adminis-

tration.

These lipoxygenase inhibitor compounds are further useful as additives to blood, blood products, blood substitutes, or other fluids which are used in artificial extracorporeal circulation or perfusion of isolated body portions, e.g., limbs and organs, whether attached to the original body, detached and being preserved or prepared for transplant, or attached to a new body. During these circulations and perfusions, aggregated platelets tend to block the blood vessels and portions of the circulation apparatus. This blocking is avoided by the presence of these compounds. For this purpose, the compound is added gradually or in single or multiple portions to the circulating blood, to the blood of the donor animal, to the perfused body portion, attached or detached, to the recipient, or to two or all of these at a total steady state dose of about 0.001 to 10 mg per liter of circulating fluid. It is especially useful to use these compounds in laboratory animals, e.g., cats, dogs, rabbits, monkeys, and rats, for these purposes in order to develop new methods and techniques for organ and limb transplants.

Hammerstrom, et al. Science 197:994-996 (1977) notes the role of 12- lipoxygenase in psoriasis. Doig, et al., Prostaglandins 20:1007-1019 (1980) and Lin, et al., J. Clin. Invest. 70:1058 (1982) disclose that 5-lipoxygenase inhibitors block platlet thrombus formation. Dawson, et al., in SRS-A and Leukotrienes, 219-226 (Wiley and Sons 1981) note that 5-lipoxygenase inhibitors block neutrophil "recruitment" during inflammatory diseases such as arthritis.

In addition, 5-lipoxygenase inhibitors prevent the production of slow-reacting substance of anaphylaxis (SRS-A), now known to be a mixture of leukotrienes. (Leukotrienes are synthesized using 5-lipoxygenase.) SRS-A mediates the symptoms and pathophysiology of asthma. See Murphy, et al., Proc. Nat. Acad. Sci. USA, 4275-4279 (1979). Thus, the 5-lipoxygenase inhibitors disclosed herein are useful in the treatment of asthma.

5-Lipoxygenase products have been implicated in essential hypertension (Chand, et al., Microcirculation 1:111-123 (1981), and gout (Rae, et al., Lancet 1122-1124 (Nov. 20, 1982), indicating that the 5-lipoxygenase inhibitors disclosed herein are useful in treating these conditions as well. Further, neutrophil depletion, such as that induced by 5-lipoxygenase inhibitors, has been shown to cause a

significant decrease in infarct size following circumflex artery occlusion. See Romson, et al., Circulation 66:85 (1982). Thus, the 5-lipoxygenase inhibitors herein may be useful in the protection of the myocardium following infarct.

The lipoxygenase inhibitors of the present invention are also useful for the prevention or treatment of deep vein thrombosis (DVT). This method comprises the administration of a compound of the Formula I to a mammal susceptible to DVT.

By "deep vein thrombosis" (DVT) is meant the thrombosis (clot formation) of the lower limb deep veins (deeply situated veins). Such thrombosis is frequently a result of major surgery, massive trauma, myocardial infarction, neoplasia, and pregnancy. The term "deep vein thrombosis" or "DVT" is meant to encompass the thrombosis resulting from these or any other causes.

By "prevention" in this context is meant the total or partial avoidance of clot formation in the deep veins of a mammal.

The present invention includes the treatment of each of various mammalian species, including humans. With respect to non-humans, the present invention is particularly and especially concerned with treating domesticated animals, for example, cattle, dogs, cats and swine. Humans are the most preferred mammals to be treated by the methods of this invention.

Any convenient route of administration is employed. Thus, oral formulation and oral administration is, for example, the preferred route for use in humans although parenteral (e.g., intravenous, intraperitoneal, and intramuscular) administration is also employed.

The dosage regimen for the lipoxygenase inhibitor compounds used to treat deep vein thrombosis will depend on a variety of factors, including the type, age, weight, sex, and medical condition of the mammal, and most importantly on the risks and probable consequences of deep vein thrombosis. It is within the skill of the attending physician or veterinarian to determine the risks of deep vein thrombosis, and to prescribe an effective amount of the lipoxygenase inhibitors claimed herein. When 1-methylthio-3-n-butyl-4-acetoxynaphthalene or 5-butyl-7-(methylthio)-4-benzofuranol-acetate are used, the dosage is in the range of about 0.01 to about 1 mg/kg/minute by intravenous infusion, or about 0.1 to about 50 mg/kg/day by oral administration. Equivalent dosages for other routes of administra-

tion are also employed. Similarly, when other lipoxygenase inhibitors are employed, equipotent doses can be administered based on the compound's comparative potency as demonstrated in the standard laboratory test.

The most preferred use of these compounds is as SRS-A inhibitors, e.g., in the treatment of asthma.

The present invention further provides a method of treating or preventing the hypersecretion of mucus in the airways or the respiratory tract of a patient in need thereof. More particularly, the present invention provides a method for treating or preventing the hypersecretion of mucus in the respiratory tract of patients with bronchial asthma, chronic bronchitis, cystic fibrosis, bronchorrhea, obstructive bronchitis and other disease conditions associated with hyperplasia of mucus secreting cells and increased mucus secretion. The method of the present invention finds particular use in warm blooded animals including mammals, such as cattle, horses, rodents, dogs, sheep, pigs, monkeys, cats, humans, and birds. The present invention provides a prophylactic as well as therapeutic method of treating hypersecretion of mucus in the airways of a warm blooded animal.

In practicing the method of treating or preventing the hypersecretion of mucus of the present invention the quantity of compound of Formula I to be administered is any amount effective in treating or preventing hypersecretion of mucus in the airways of the patient being treated. The compounds of Formula I are administered, e.g., intravenously, intramuscularly, topically, by aerosol inhalation, bucally or orally. The quantity of compound of Formula I effective in achieving the method here claimed is determined by the particular mode of administration and frequency of administration as well as the age and condition of the patient. Generally the amount of compound administered will range from about 0.001 mg to 10 mg per dose given up to three times per day by aerosol inhalation, with a range from about 0.01 mg to 10 mg per dose being preferred. For intravenous administration a dose of about 0.01 to 10 μg/kg/min is administered with intramuscular injection ranging from 0.5 to 15 mg per dose. For oral administration unit doses of from 1 mg to 100 mg given up to three times per day of compounds of Formula I are effective in practicing the method of the present invention. The quantity of compound

applied topically is that which will give comparable blood levels of active ingredient when said substance is administered by any of the other various routes of administration.

In practicing the method of treating or preventing the hypersecretion of mucus, the compounds of Formula I are formulated into compositions for administration to humans and animals in unit dosage forms, such as tablets, capsules, pills, powders, granules, sterile parenteral solutions or suspensions, eye drops, oral solutions or suspensions, and oil in water and water in oil emulsions containing suitable quantities of the compound.

For oral administration, either solid or fluid unit dosage forms can be prepared. For preparing solid compositions such as tablets, the compound of Formula I is mixed with conventional ingredients such as talc, magnesium stearate, dicalcium phosphate, magnesium aluminum silicate, calcium sulfate, starch, lactose, acacia, methylcellulose, and functionally similar materials as pharmaceutical diluents or carriers. Capsules are prepared by mixing the compound with an inert pharmaceutical diluent and filling the mixture into a hard gelatin capsule of appropriate size. Soft gelatin capsules are prepared by machine encapsulation of a slurry of the compound with an acceptable vegetable oil, light liquid petrolatum or other inert oil.

Fluid unit dosage forms for oral administration such as syrups, elixirs, and suspensions can be prepared. The forms can be dissolved in an aqueous vehicle together with sugar, aromatic flavoring agents and preservatives to form a syrup. An elixir is prepared by using a hydroalcoholic (ethanol) vehicle with suitable sweeteners such as sugar and saccharin, together with an aromatic flavoring agent.

Suspensions can be prepared with an aqueous vehicle with the aid of a suspending agent such as acacia, tragacanth, methylcellulose and the like.

For parenteral administration, fluid unit dosage forms are prepared utilizing the compound and a sterile vehicle, water being preferred. The pharmaceutically useful compound described herein, depending on the vehicle and concentration used, can be either suspended or dissolved in the vehicle. In preparing solutions the compound can be dissolved in water for injection and filter sterilized before filling into a suitable vial or ampoule and sealing. Advantageously, adjuvants such as a local anesthetic, preservative and

buffering agents can be dissolved in the vehicle. To enhance the stability, the composition can be frozen after filling into the vial and the water removed under vacuum. The dry lyophilized powder is then sealed in the vial and an accompanying vial of water for injection is supplied to reconstitute the liquid prior to use. Parenteral suspensions can be prepared in substantially the same manner except that the compound is suspended in the vehicle instead of being dissolved and sterilization cannot be accomplished by filtration. These compounds can be sterilized by exposure to ethylene oxide or an equivalent gas before suspending in the sterile vehicle. Advantageously, a surfactant or wetting agent is included in the composition to facilitate uniform distribution of the compound.

Compositions for inhalation useful in practicing the method of present invention are of three basic types: (1) a powder mixture preferably micropulverized with particle size, preferably from about 2 to 5 microns; (2) an aqueous solution to be sprayed with a nebulizer; (3) an aerosol with volatile propellant in a pressurized container.

The powders are quite simply prepared by mixing a suitable pharmaceutically useful compound of Formula I with a solid base which is compatible with lung tissue, preferably lactose. The powders are packaged in a device adapted to emit a measured amount of powder when inhaled through the mouth.

Aqueous solutions are prepared by dissolving the appropriate compound of the Formula I in water and adding salt to provide an isotonic solution and buffering to a pH compatible with inhalation. The solutions are dispersed in a spray device or nebulizer and sprayed into the mouth while inhaling.

Aerosols are prepared by dissolving an appropriate pharmaceutically useful compound of Formula I in water or ethanol and mixing with a volatile propellant and placing in a pressurized container having a metering valve to release a predetermined amount of material.

The liquefied propellant employed is one which has a boiling point below 65°F at atmospheric pressure. For use in compositions intended to produce aerosols for medicinal use, the liquefied propellant should be non-toxic. Among the suitable liquefied propellants which may be employed are the lower alkanes containing up to 5

carbon atoms, such as butane and pentane, or a lower alkyl chloride, such as methyl, ethyl or propyl chlorides. Further suitable liquefied propellants are the fluorinated and fluorochlorinated lower alkanes or mixtures thereof, such as, dichlorodifluoromethane, dichlorotetrafluoroethane, trichloromonofluoromethane, dichloromonofluoromethane, monochlorodifluoromethane, trichlorotrifluoroethane, difluoroethane and monochlorotrifluoromethane.

Generally, the compounds can be prepared by reaction of the appropriate chromium carbene complex with an alkyne. However, the reaction conditions vary when W is OCH_3 or $S(O)_qY$.

Where W is OCH_3 the reaction can proceed as shown in Scheme A in the presence of Ac_2O (1-2 mol eq) and NEt_3 (1-2 mol eq) to yield the compound. In the absence of Ac_2O and NEt_3, R_3 will be a hydrogen.

Where W is $S(O)_qY$ the compound of the present invention can be prepared by the method depicted in Scheme B wherein q=0.

The chemistry requires that the initial cycloaddition reaction (A1 to A2) generate a product where q=0 that is the thioalkyl derivative. A second oxidation step is required to obtain the $S(O)_qY$ group where q is greater than zero. Methods for conducting the oxidation of a SY group are well known such as N.J. Leonard, C.R. Johnson, J. Org. Chem., 27, 282 (1962). One method can comprise treatment with potassium peroxymonosulfate to prepare the SO_2Y group.

In Scheme B, a carbene complex of the Formula A-1 is reacted with an acetylene of the Formula A-2 (preferably 1.5 equivalents). The cycloaddition of the carbene complex A-1 having the $-S(O)_qY$ group forms the subject product only when $BF_3 \cdot Et_2O$ (5 mol eq), Ac_2O (5 mol eq) and NEt_3 (5 mol eq) are present. Conversion of the Ac group to the OH then introduction of the OR_3 group can be done by any conventional means.

Both Scheme A and B reactions are preferably undertaken in a solvent such as tetrahydrofuran (THF) in an inert atmosphere (e.g., argon). Preferably, the reaction temperature is at about 65° C.

The process for preparing the subject compounds is described more fully in the Examples given below. The carbene complexes within the scope of Formula A-1 are well known and readily available or may be prepared by known means. Thus, pentacarbonyl[aryl(methoxy)carbene]chromium wherein the aryl moiety is phenyl, 2-(N-methylpyrrolyl), 2-furyl, or 2-thienyl are described in E.O. Fisher, J.

Organometal. Chem. 16:29 (1969); K.H. Dotz, et al., Chem. Ber. 111:2517 (1978); A. Yamashita, et al., Tet. Lett. 23:3765 (1982); and Citilam, et al., Inorg. Synth. 17:95 (1977). Alternatively, the Al carbene complex can be prepared as shown in Method "a" and Method "b".

The alkynes are well known, readily available compounds or may be prepared by known means. Formation of the acetylated product A-2 where W is OCH_3 is known, for example, see U.S. Patent 4,737,519, Col. 13 through Col 14, herein incorporated by reference.

The present invention is seen more fully by the Examples given below.

Preparation of various A-1 carbene complex, starting materials, for reaction in Scheme B were prepared as follows in Examples 1-5.

Final preparation of the subject compound was preformed as explained in Scheme B using the various A-2 carbene complexes. Examples 6-9 show the preparation of various A-2 intermediates which can be reacted to form the final end product as explained in Scheme B. Examples 10-11 show the preparation of the subject compound where W is OCH_3, Scheme A.

Example 1 Preparation of Pentacarbonyl[phenyl(ethylthiol)carbene]chromium from Tetra-n-butylammonium-Pentacarbonyl(phenyl)chromate.

In a 100 ml round bottom flask, equipped with a stirring bar, an addition funnel with a three-way argon-vacuum inlet was placed 0.5 grams of the tetra-n-butylalkoxide carbene. The flask was evacuated and filled with argon three times prior to CH_2Cl_2 addition (38 ml). To an addition funnel was introduced a solution of 0.07 ml of acetyl chloride in 8 ml of CH_2Cl_2. The carbene solution was cooled to -40° C and the acetyl chloride solution was added dropwise with vigorous stirring (the funnel was rinsed with CH_2Cl_2 upon complete addition). The solution was stirred at -40° C for one hour, then cooled to -78° C. To an addition funnel was introduced a solution of 0.08 ml of ethane thiol in 8 ml of CH_2Cl_2. The ethane thiol solution was added dropwise to the carbene solution with vigorous stirring and the funnel was rinsed with CH_2Cl_2. The solution was allowed to stir at-78° C for one hour, then the cooling bath was removed. After the solution was warmed to 25° C, the solvent was removed by rotary evaportaion and the crude product was purified by short path column

chromatography (26 grams of silica gel). Elution by ethyl ether gave 0.28 grams (88%) of the ethylthiol phenyl carbene compound.

Example 2 Preparation of Pentacarbonyl[phenyl(ethylthiol)carbene]chromium from Tetraethylammonium-Pentacarbonyl-(phenyl)chromate.

In a 100 ml round bottom flask, equipped with a stirring bar, an addition funnel with a three-way argon-vacuum inlet was placed 0.8 grams of the tetra ethylalkoxide carbene and the flask was evacuated and filled with argon three times prior to CH_2Cl_2 addition (35 ml). To an addition funnel was introduced a solution of 0.09 ml of acetyl chloride in 8 ml of CH_2Cl_2, then the carbene solution was cooled to-40° C before the acetyl chloride solution was added dropwise with vigorous stirring (the funnel was rinsed with CH_2Cl_2 upon complete addition). The resulting solution was stirred at -40° C for one hour, then cooled to -78° C. To an addition funnel was introduced a solution of 0.1 ml of ethane thiol in 8 ml of CH_2Cl_2. The ethane thiol solution was added dropwise to the carbene solution with vigorous stirring and the funnel was rinsed with CH_2Cl_2. The solution was allowed to stir at -78° C for one hour prior to the removal of the bath. After the solution was warmed to 25° C, the solvent was removed by rotary evaporation and the crude product was purified by flash column chromatography (28 grams of silica gel). Elution by diethyl ether gave 0.28 grams (70%) of the phenyl(ethylthiol)chromium carbene complex.

Example 3 Preparation of Pentacarbonyl[phenyl(ethylthiol)carbene]chromium from Tetra-n-propylammonium-Pentacarbonyl(phenyl)chromate.

In a 100 ml round bottom flask, equipped with a stirring bar, an addition funnel with a three-way argon-vacuum inlet was placed 0.8 grams of the tetra-n-propylalkoxide carbene and the flask was evacuated and filled with argon three times prior to CH_2Cl_2 addition (35 ml). To an addition funnel was introduced a solution of 0.08 ml of acetyl chloride in 8 ml of CH_2Cl_2. The carbene solution was cooled to -40° C before the acetyl chloride solution was added dropwise with vigorous stirring (the funnel was rinsed with CH_2Cl_2 upon complete addition). The resulting solution was stirred at -40° C for one hour, then cooled to -78° C. To an addition funnel was introduced a solution of 0.08 ml of ethane thiol in 8 ml of CH_2Cl_2.

The ethane thiol solution was added dropwise to the carbene solution with vigorous stirring and the funnel was rinsed with CH_2Cl_2. The solution was allowed to stir at -78° C for one hour prior to the removal of the bath. After the solution had warmed to 25° C, the solvent was removed by rotary evaporation and the crude product was purified by flash column chromatography (28 grams of silica gel). Elution by diethyl ether gave 0.28 grams (83%) of the phenyl(ethylthiol)chromium carbene complex.

Example 4 Preparation of Pentacarbonyl[phenyl(ethylthiol)carbene]chromium from Tetramethylammonium-Pentacarbonyl(phenyl)chromate.

In a 100 ml round bottom flask, equipped with a stirring bar, an addition funnel with a three-way argon-vacuum inlet was placed 0.8 grams of the tetra-methylalkoxide carbene and the flask was evacuated and filled with argon three times prior to CH_2Cl_2 addition (35 ml). To an addition funnel was introduced a solution of 0.11 ml of acetyl chloride in 8 ml of CH_2Cl_2. The carbene solution was cooled to -40° C before the acetyl chloride solution was added dropwise with vigorous stirring (the funnel was rinsed with CH_2Cl_2 upon complete addition). The resulting solution was stirred at -40° C for one hour, then cooled to -78° C. To an addition funnel was introduced a solution of 0.11 ml of ethane thiol in 8 ml of CH_2Cl_2 and the ethane thiol solution was added dropwise to the carbene solution with vigorous stirring and the funnel was rinsed with CH_2Cl_2. The solution was allowed to stir at -78° C for one hour prior to the removal of the bath. After the solution was warmed to 25° C, the solvent was removed by rotary evaporation and the crude product was purified by flash column chromatography (28 grams of silica gel). Elution by diethyl ether gave 0.37 grams (80%) of the phenyl ethylthiol chromium carbene complex.

Example 5 Preparation of Pentacarbonyl[phenyl(methylthiol)carbene]chromium from Tetra-n-butylammonium-Pentacarbonyl(phenyl)chromate.

In a 1000 ml round bottom flask, equipped with a stirring bar, an addition funnel with a three-way argon-vacuum inlet was placed 27 grams of the tetra-n-butylalkoxide carbene and the flask was evacuated and filled with argon three times prior to CH_2Cl_2 addition (400 ml). To an addition funnel was introduced a solution of 3.9 ml of

acetyl chloride in 80 ml of CH_2Cl_2. The carbene solution was cooled to -40° C before the acetyl chloride solution was added dropwise with vigorous stirring (the funnel was rinsed with CH_2Cl_2 upon complete addition). The resulting solution was stirred at -40° C for one hour, then cooled to -78° C. To an addition funnel was introduced a solution of 3.0 ml of methane thiol in 80 ml of CH_2Cl_2. The methane thiol solution was added dropwise to the carbene solution with vigorous stirring and the funnel was rinsed with CH_2Cl_2. The solution was allowed to stir at -78° C for one hour prior to the removal of the bath. After the solution was warmed to room temperature, the solvent was removed by rotary evaporation and the crude product was purified by flash column chromatography (300 grams of silica gel). Elution by diethyl ether gave 13 grams (70%) of the phenyl methylthiol chromium carbene complex.

Example 6 Preparation of 1-Ethylthio-3-n-butyl-4-acetoxy-naphthalene.

To a 200 ml three-necked round bottom flask with a stirring bar, an argon-vacuum inlet and two rubber septa was added 3.0 g of the thio carbene. The system was evacuated and filled with argon three times prior to THF addition (600 ml). This was followed by treatment with Ac_2O (4.1 ml), Et_3N (6.1 ml), $BF_3 \cdot OEt_2$ (8.4 ml) and 1-hexyne (2 ml). The solution was heated to 65° C for 3 days under argon, after which the solvent was removed by rotary evaporation. The crude product was purified by flash chromatography, using 10% ether in hexane as the eluent, to give 1.8 g of the oily naphthalene product.

Example 7 Preparation of 1-Ethylsulfonyl-3-n-butyl-4-acetoxy-naphthalene.

To a 500 ml round bottom flask with a stirring bar was added 0.6 g of the sulfide dissolved in MeOH (50 ml). The solution was stirred vigorously while a solution consisting of Oxone (1.83 g) in 100 ml of pH 7 buffer was added. After 4 hours, 400 ml of water was added and the aqueous solution was extracted with 4 x 100 ml portions of CH_2Cl_2. The extracts were dried over Na_2SO_4, filtered, concentrated and purified via flash chromatography using 30% ether in n-hexane as the eluent, to give 0.65 g (98%) of the sulfone. The product was further purified by recrystallization using ether/hexane, m.p. 109° C.

Example 8 Preparation of 1-Methylthio-3-n-butyl-4-acetoxy naphthalene.

In a 1000 ml three-necked round bottom flask, with a stirring bar, an argon-vacuum inlet and two rubber septa. was added 4.0 g of the thiocarbene. The flask was evacuated and filled with argon three times prior to THF addition (400 ml). This was followed by treatment with Ac_2O (2.2 ml), Et_3N (3.4 ml), $BF_3 \cdot OEt_2$ (1.8 ml) and 1-hexyne (2.8 ml). The solution was heated to 65° C for 3 days under argon, after which the solvent was removed by rotary evaporation. The crude product was purified by flash chromatography, using 10% ether in hexane as the eluent, to give 1.8 g (44%) of the product. This product was further purified by recrystallization using ether/-pentane, m.p. 89° C.

Example 9 Preparation of 1-Methylsulfonyl-3-n-butyl-4-acetoxy-naphthalene.

To a 500 ml round bottom flask with a stirring bar was added 0.6 g of sulfide dissolved in MeOH (50 ml). The solution was stirred vigorously while a solution consisting of Oxone (1.83 g) in 100 ml of pH 7 buffer was added. After 4 hours, 400 ml of water was added, and the aqueous solution was extracted with 4 x 100 ml portions of CH_2Cl_2. The extracts were dried with Na_2SO_4, filtered, concentrated and purified via flash chromatography using 30% ether in n-hexane as the eluent, to give 0.63 g (95%) of the sulfone. The product was further purified by recrystallization using ether/hexane, m.p. 107° C.

Example 10 Preparation of 5,6-Diethyl-4-hydroxy-7-methoxy-2-methylbenzofuran.

Preparation of Pentacarbonyl[5-methyl-2-furyl(methoxy)carbenechromium

To a cooled (-78° C, dry ice-acetone bath) solution of 2-methyl-furan in THF, prepared under argon, was added dropwise n-BuLi (n-hexane solution) via syringe under argon over a period of 20 min. The resulting solution was warmed up to 25° C over a period of 6 hrs, and stirred at 25° C for 15 hrs under argon. The resulting yellow solution was introduced to the suspension of $Cr(CO)_6$ in dry ether, prepared under argon, using a liquid transferring cannula at 25° C under argon. The deep red solution was stirred at 25° C for an additional 1 hr, then the solvent was removed by rotary evaporation. The dark brown residue was dissolved in 200 ml H_2O, and $Me_3O \cdot BF_4$ was

portionwise added to the aqueous solution. The aqueous layer was extracted with ether (3 x 400 ml) and the extracts were combined, washed with saturated $NaHCO_3$ aq sol. (2 x 300 ml), sat. NaCl aq sol. (3 x 300 ml), dried over anhydrous Na_2SO_4, filtered and concentrated. The dark brown residue was chromatographed using flash column (silica gel 600 g). Elution by 5-10% ether in n-hexane isolated 19.8 g (62.6%) of Pentacarbonyl[5-methyl-2-furyl(methoxy)carbene]chromium as dark purple red solid.

A solution of the carbene complex and 3-hexyne in DMF, prepared under argon at 25° C, was heated at 125-130° C (bath temperature) for 6 hrs, then 100° C (bath temperature) for 15 hrs under argon. The reaction mixture was cooled and diluted with 500 ml of ether. The ether layer was washed with sat. NaCl aq sol. (3 x 250 ml). The solvent was removed by rotary evaporation and the residue was treated with 1N HCl aq sol. (10 ml), CH_2Cl_2 (20 ml), and MeOH (150 ml) at 25° C for 5 hrs. The solvent ws removed by rotary evaporation and the residue was dissolved in 500 ml ether. The ether layer was washed with sat. NaCl aq sol. (2 x 200 ml), dried over anhydrous $MgSO_4$, filtered and concentrated. The residue was chromatographed using a silica gel (400 g used) flash column. Elution by 20-30% ether in n-hexane isolated 1.00 g (54.1%) of 5,6-diethyl-4-hydroxy-7-methoxy-2-methylbenzofuran as yellow oil.

The IC_{50} data for this compound is shown in Table 1, Compound 7.

Example 11 Preparation of 5-n-Butyl-4-hydroxy-7-methoxy-2-methylbenzofuran.

The carbene complex as prepared in the first step of Example 10 was mixed with 1-hexyne in DMF under argon at 25° C and was heated at 125-130° C (bath temperature) for 6 hrs, then 100° C (bath temperature) for 15 hrs under argon. The reaction mixture was cooled and diluted with 800 ml of ether. The ether layer was washed with sat. NaCl aq sol. (3 x 300 ml). The solvent was removed by rotary evaporation, and the residue was treated with 1N HCl aq sol. (25 ml), CH_2Cl_2 (400 ml), and MeOH (350 ml) at 25° C for 5 hrs. The solvent was removed by rotary evaporation and the residue was dissolved in 800 ml ether. The ether layer was washed with sat. NaCl aq sol. (2 x 300 ml), dried over anhydrous $MgSO_4$, filtered and concentrated. The residue was chromatographed using a silica gel (400 g used) flash column. Elution by 20% ether in n-hexane gave the product as a white

solid.

The IC_{50} data for this compound is shown in Table I, Compound 8.

Various forms of the subject compounds were evaluated using standard assay procedures (see, Adv. Enzymology, 58, "Enzymology and Physiology of Reticulocyte Lipoxygenase:Comparison with other Lipoxygenases", pp. 192-263 (1986)) to measure their inhibition of 5-lipoxygenase (5-Lo), 15-lipoxygenase (15-Lo), and thromboxane-B_2 (TxB_2). These results are shown in Table 1 as a measure of 50% inhibition concentration (IC_{50}) in micrograms per milliliter ($\mu g/ml$).

TABLE 1

Compound							IC_{50} in μ/ml		
#	R_3	R_2	R_1	W	D	Z	5-Lo	15-Lo	TxB_2
1	CH_3	$COCH_3$	OH	SCH_3	O	H	-	20	-
2	$COCH_3$	n-C_4H_9	H	SCH_3	O	H	0.05	0.07	1.88
3	$COCH_3$	C_6H_5	H	SCH_3	O	H	0.10	0.05	2.51
4	$COCH_3$	n-C_4H_9	H	SCH_3	CH=CH	H	0.09	-	0.59
5	$COCH_3$	n-C_4H_9	H	SO_2CH_3	CH=CH	H	1.02	-	1.55
6	$COCH_3$	C_6H_5	H	SCH_3	CH=CH	H	0.15	0.15	8.95
7	H	C_2H_5	C_2H_5	OCH_3	O	CH_3	0.07	1.03	6.31
8	H	n-C_4H_9	H	OCH_3	O	CH_3	0.01	0.64	2.52

Table 2 shows 15-lipoxygenas (15-Lo) inhibition data for various compounds at a 20 μg/ml unit dose. The negative values indicate a percentage increase in 15-Lo products. This result is indicative of an increased production of materials which cross react with the 15-HETE antibodies.

TABLE 2

Compound							15-Lo
#	R_3	R_2	R_1	W	D	Z	20μg/ml Unit Dose % Inhibition
1	$COCH_3$	$CH=CH_2$	OC_2H_5	SCH_3	O	H	54.5
2	CH_3	$COCH_3$	OH	SCH_3	O	H	45.5
3	$COCH_3$	C_2H_5	C_2H_5	SCH_3	O	H	-122.7
4	$COCH_3$	C_6H_5	C_6H_5	SCH_3	O	H	-227.3
5	$COCH_3$	C_6H_5	CH_3	SCH_3	O	H	-286.4
6	$COCH_3$	C_6H_5	$CO_2C_2H_5$	SCH_3	O	H	-36.4
7	$COCH_3$	C_6H_5	$CO_2C_2H_5$	SCH_3	CH=CH	H	-59.1
9	$COCH_3$	C_2H_5	C_2H_5	SCH_3	CH=CH	H	-15.4
10	$COCH_3$	C_6H_5	CH_3	SCH_3	CH=CH	H	-84.6

Table 3 shows 15-lipoxygenase inhibition data (15-Lo) for a set of compounds at various unit doses in μg/ml

TABLE 3

Compound							15-Lo	
#	R_3	R_2	R_1	W	D	Z	Unit Dose μG/ml	% Inhibition
1	$COCH_3$	$CH=CH_2$	OC_2H_5	SCH_3	O	H	0.2	30
							2.0	36
							20.0	35
2	$COCH_3$	C_4H_9	H	SCH_3	O	H	0.2	58
							2.0	73
							2.0	100
3	$COCH_3$	C_6H_5	H	SCH_3	O	H	0.2	63
							2.0	85
							20.0	99
4	$COCH_3$	C_6H_5	H	SCH_3	CH=CH	H	0.2	54
							2.0	84
							20.0	80

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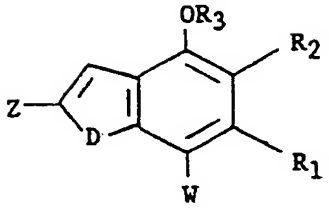

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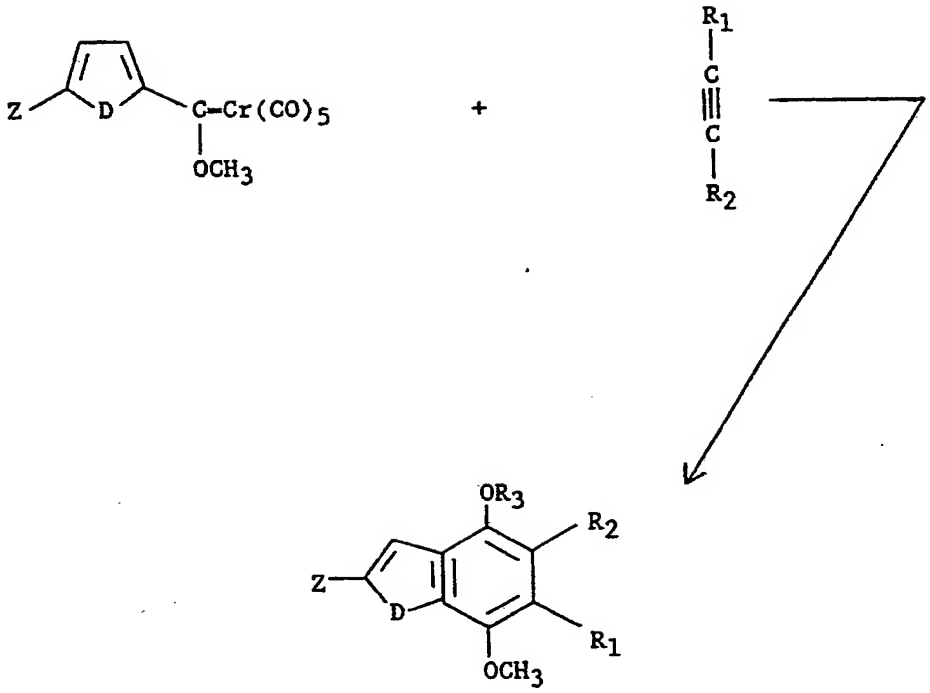

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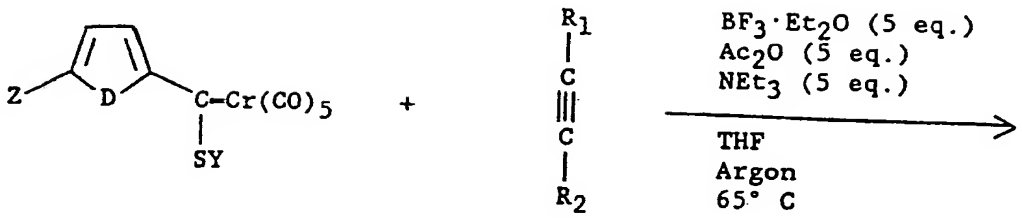

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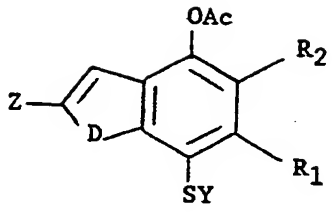

A2

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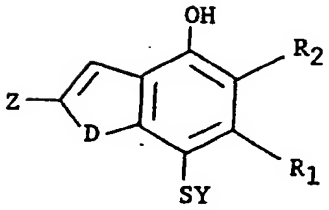
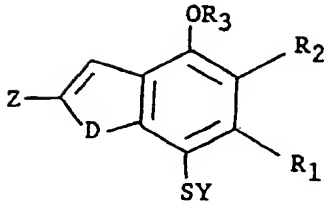
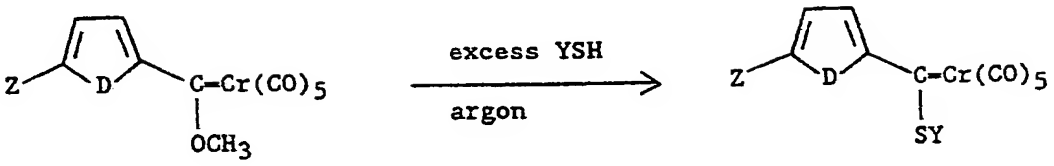




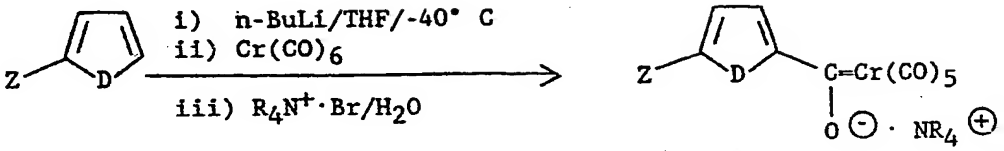
SCHEME B (continued)

Method a

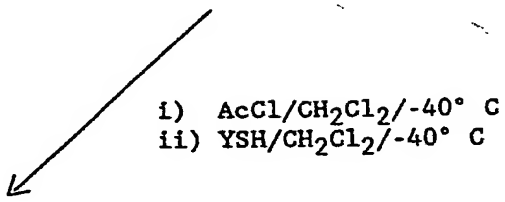


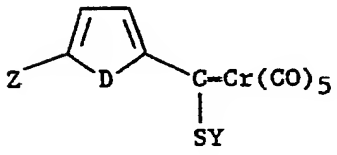
Al

Method b



R_4=Me, Et, n-Pro, n-Bu





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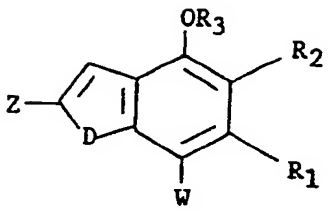
CLAIMS

1. A compound of the Formula I



I

or a pharmacologically acceptable acid addition salt thereof wherein R_1 and R_2 are the same or different and are

(a) hydrogen,

(b) (C_1-C_{10})alkyl,

(c) (C_2-C_{10})alkenyl, or

(d) PhX;

wherein (PhX) is phenyl substituted by zero to 3 of the following:

(a) (C_1-C_4)alkyl,

(b) chloro,

(c) fluoro,

(d) bromo,

(e) nitro,

(f) trifluoromethyl; or

(g) OR_4;

wherein D is

(a) -CH=CH-,

(b) $-N(CH_3)$,

(c) -S-, or

(d) -O-;

wherein R_3 is

(a) CH_3-C(O)-,

(b) hydrogen,

(c) $-C(O)-(CR_{17}R_{18})_m-(CH_2)_n-NR_{14}R_{15}$,

(d) -C(O)-AA, or

(e) $-C(O)-PhX-NH_2$;

wherein m is 1, 2, 3, or 4;

wherein n is 0, 1, 2, 3, 4, or 5;

wherein -C(O)AA is the acyl portion derived from any naturally occurring alpha-amino acid;

wherein R_{14} and R_{15} are the same or different and are:

(a) hydrogen,

(b) (C_1-C_{10}) alkyl,

(c) -C(O)R_{16},

(d) -C(O)-PhX, or

(e) -PhX;

with the proviso that R_{14} and R_{15} are other than hydrogen when n is zero;

wherein R_{16} is (C_1-C_4) alkyl;

wherein R_{17} and R_{18} are the same or different and are:

(a) hydrogen,

(b) (C_1-C_{10}) alkyl,

(c) -CH_2-PhX, or

(d) -PhX;

with the proviso that each occurrence of R_{17} and R_{18} is the same or different;

wherein PhX-NH_2 is an amino-substituted phenyl group additionally substituted by zero to 3 of the following:

(a) (C_1-C_4) alkyl,

(b) chloro,

(c) fluoro,

(d) bromo,

(e) nitro,

(f) trifluoromethyl, or

(g) OR_4;

wherein R_4 is

(a) hydrogen, or

(b) (C_1-C_4)alkyl;

wherein W is

(a) OCH_3 or

(b) $S(O)_qY$;

wherein q is 0, 1 or 2;

wherein Y is

(a) (C_1-C_4)alkyl,

(b) (C_1-C_4) alkenyl,

(c) PhX;

wherein W is $S(O)_qY$ then Z is

(a) hydrogen or

(b) (C_1-C_4)alkyl;

wherein W is OCH_3 then Z is (C_1-C_4)alkyl;

with a proviso where Z is hydrogen, D is ethylene and where R_1 and R_3 are hydrogen, R_2 is phenyl, and W is SCH_3 or SPh; or where R_1 and R_2 are methyl, R_3 is hydrogen and W is SCH_3; or where R_1 is hydrogen, R_2 is phenyl, R_3 is $COCH_3$ and W is SCH_3.

2. The compound of Claim 1 wherein R_3 is CH_3 or $COCH_3$.

3. The compound of Claim 1 wherein R_2 is selected from the group consisting of $COCH_3$, C_6H_5, C_2H_5, $CH=CH_2$ and C_4H_9.

4. The compound of Claim 1 wherein R_1 is selected from the group consisting of hydrogen, OH, OC_2H_5, C_2H_5, CH_3, $CO_2C_2H_5$.

5. The compound of Claim 1 wherein D is oxygen or CH=CH.

6. The compound of Claim 1 wherein Z is hydrogen.

7. The compound of Claim 1 wherein W is $S(O)_qY$ wherein q is 0 and Y is CH_3.

8. The compound of Claim 1 which is

a) 5-ethenyl-6-ethoxy-7-(methylthio)-4-benzofuranol acetate;

b) 1-[6-hydroxy-4-methoxy-7-(methylthio)-5-benzofuranyl]-ethanone;

c) 5-butyl-7-(methylthio)-4-benzofuranol acetate;

d) 7-(methylthio)-5-phenyl-4-benzofuranol acetate;

e) 4-(methylthio)-2-phenyl-1-naphthalenol acetate;

f) 2-butyl-4-(methylthio)-1-naphthalenol acetate; or

g) 2-butyl-4-(methylsulfonyl)-1-naphthalenol acetate.

9. The compound of Claim 1 wherein W is OCH_3.

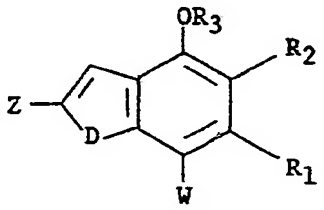
10. The compound of Claim 9 which is

(a) 5,6-diethyl-4-hydroxy-7-methoxy-2-methylbenzofuran; or

(b) 5-n-butyl-4-hydroxy-7-methoxy-2-methylbenzofuran.

11. A method for treating or preventing the hypersecretion of mucus in the respiratory tract of a patient in need thereof which comprises:

administering to said patient in an amount effective to treat or prevent said hypersecretion of mucus a compound of Formula I



I

or a pharmacologically acceptable acid addition salt thereof;

wherein R_1 and R_2 are the same or different and are

(a) hydrogen,

(b) $(C_1\text{-}C_{10})$alkyl,

(c) $(C_2\text{-}C_{10})$alkenyl, or

(d) PhX;

wherein (PhX) is phenyl substituted by zero to 3 of the following:

(a) $(C_1\text{-}C_4)$alkyl,

(b) chloro,

(c) fluoro,

(d) bromo,

(e) nitro,

(f) trifluoromethyl; or

(g) OR_4;

wherein D is

(a) -CH=CH-,

(b) $-N(CH_3)$,

(c) -S-, or

(d) -O-;

wherein R_3 is

(a) $CH_3\text{-}C(O)$-,

(b) hydrogen,

(c) $-C(O)-(CR_{17}R_{18})_m-(CH_2)_n-NR_{14}R_{15}$,

(d) -C(O)-AA, or

(e) $-C(O)-PhX-NH_2$;

wherein m is 1, 2, 3, or 4;

wherein n is 0, 1, 2, 3, 4, or 5;

wherein -C(0)AA is the acyl portion derived from any naturally occurring alpha-amino acid;

wherein R_{14} and R_{15} are the same or different and are:

(a) hydrogen,

(b) (C_1-C_{10}) alkyl,

(c) -C(0)R_{16},

(d) -C(0)-PhX, or

(e) -PhX;

with the proviso that R_{14} and R_{15} are other than hydrogen when n is zero;

wherein R_{16} is (C_1-C_4) alkyl;

wherein R_{17} and R_{18} are the same or different and are:

(a) hydrogen,

(b) (C_1-C_{10}) alkyl,

(c) -CH_2-PhX, or

(d) -PhX;

with the proviso that each occurrence of R_{17} and R_{18} is the same or different;

wherein PhX-NH_2 is an amino-substituted phenyl group additionally substituted by zero to 3 of the following:

(a) (C_1-C_4) alkyl,

(b) chloro,

(c) fluoro,

(d) bromo,

(e) nitro,

(f) trifluoromethyl, or

(g) OR_4;

wherein R_4 is

(a) hydrogen, or

(b) (C_1-C_4)alkyl;

wherein W is

(a) OCH_3 or

(b) $S(O)_qY$

wherein q is 0, 1 or 2;

wherein Y is

(a) (C_1-C_4)alkyl,

(b) (C_1-C_4) alkenyl,

(c) PhX;

wherein W is $S(O)_qY$ then Z is

(a) hydrogen; or

(b) (C_1-C_4)alkyl;

wherein W is OCH_3 then Z is (C_1-C_4) alkyl;

wherein D is -CH=CH- then Z is hydrogen;

with a proviso where D is -CH=CH- or $=N(CH_3)$ and Z is hydrogen, and where D is O or -CH=CH-, R_3 is $COCH_3$, Z is hydrogen and R_1 and R_2 are both ethyl, phenyl or a phenyl and a methyl or an ethyl ester.

INTERNATIONAL SEARCH REPORT

International Application No PCT/US 89/03492

I. CLASSIFICATION OF SUBJECT MATTER (if several classification symbols apply, indicate all) [6]

According to International Patent Classification (IPC) or to both National Classification and IPC

IPC[5]: C 07 D 317/22, 323/21, 307/86, 307/79, A 61 K 31/34, 31/22

II. FIELDS SEARCHED

Minimum Documentation Searched [7]

Classification System	Classification Symbols
IPC[5]	C 07 D 307/00, C 07 C 317/00, C 07 C 323/00

Documentation Searched other than Minimum Documentation to the Extent that such Documents are Included in the Fields Searched [8]

III. DOCUMENTS CONSIDERED TO BE RELEVANT [9]

Category [10]	Citation of Document, [11] with indication, where appropriate, of the relevant passages [12]	Relevant to Claim No. [13]
X	EP, A, 0146348 (UPJOHN) 26 June 1985, see the whole document (cited in the application)	1-10
X	EP, A, 0165810 (MERCK FROSST CANADA) 27 December 1985, see the whole document	1-10
X	EP, A, 0201071 (DU PONT DE NEMOURS) 12 November 1986, see the whole document	1-10
X	Chemical Abstracts, vol. 85, no. 23, 6 December 1976, (Columbus, Ohio, US), B.S. Patwa et al.: "Fries reaction. Part XII: Preparation of hydroxydiaryl-sulfones", see page 484, abstract 177000f & J. Indian Chem. Soc. 1976, 53(6), 602-3	1-10
X	Chemical Abstracts, vol. 69, no. 11, 9 September 1968, (Columbus, Ohio, US), Ukai, Shigeo et al.: "Reaction of phenol	1-10

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* Special categories of cited documents: [10]

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

IV. CERTIFICATION

Date of the Actual Completion of the International Search	Date of Mailing of this International Search Report
21st November 1989	03.01.90
International Searching Authority	**Signature of Authorized Officer**
EUROPEAN PATENT OFFICE	F.M. VRIJDAG

III. DOCUMENTS CONSIDERED TO BE RELEVANT (CONTINUED FROM THE SECOND SHEET)

Category *	Citation of Document, with indication, where appropriate, of the relevant passages	Relevant to Claim No
	derivatives with sulfoxides (including reactions involving sulfides and hydrogen peroxide). IV. Synthesis of 4-thio-substituted 1,2-naphthoquinone derivatives", see pages 4083,4084, abstract 43645f & Chem. Pharm. Bull. (Tokyo) 1968, 16(4), 606-12	
X	Liebigs Annalen der Chemie, no. 2, 1985, VCH Verlagsgesellschaft mbH (Weinheim, DE) H. Laatsch: "Über die Selektivität der Addition von Diazomethan an benzoid substituierte 1,4-Naphthochinone" pages 251-274, see page 253, compound 15b	1-10
X	Journal of the Chemical Society, Perkin Transactions I, 1983 K. Buggle et al.: "Ring-expansion of 3-arylinden-1-ones with lithium methylsulphinylmethanide" pages 2075-2076, see page 2076, compound 7a	1-10
X	Chemical Abstracts, vol. 95, no. 23, 7 December 1981, (Columbus, Ohio, US), D.B. Saxena et al.: "Synthesis and insecticidal activity of O,O-diethyl -(4-thiomethyl-1-naphthyl)phosphate" see page 647, abstract 203603h & Pesticides 1981, 15(8), 14-15	1-10
X	Chemical Abstracts, vol. 95, no. 5, 3 August 1981, (Columbus, Ohio, US), S.X. Yang et al.: "Studies on certain thiophosphatic insecticides containing naphthalene rings" see page 724, abstract 42730e & Kao Teng Hsueh Hsiao Hua Hsueh Hsueh Pao 1981, 2(1), 55-62	1-10
X	Chemical Abstracts, vol. 90, no. 5, 29 January 1979, (Columbus, Ohio, US), G. Mann et al.: "Oxidative coupling of CH-acidic compounds with p-phenylenediamines. I. Influence of substituents in CH-acidic compounds on the color coupling", see page 436, abstract 38324e & J. Prakt. Chem. 1978, 320(5), 705-14	1-10

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III. DOCUMENTS CONSIDERED TO BE RELEVANT (CONTINUED FROM THE SECOND SHEET)

Category *	Citation of Document, with indication, where appropriate, of the relevant passages	Relevant to Claim No
X	Chemical Abstracts, vol. 68, no. 21, 20 May 1968, (Columbus, Ohio, US), V.A. Koptyug et al.: "Effect of substituents in isomeric compounds. VI. Dissociation constants for hydroxy-napththyl methyl sulfones" see page 916, abstract 95225t & Zh. Org. Khim. 4(1), 15-19, 1968 --	1-10
X	Journal of the Chemical Society, Perkins Transcations I, 1975 K. Buggle et al.: "Decomposition products of pyrazolines formed from 3-alkylthioinden-1-ones and diazomethane" pages 572-575, see page 573, compound VIIa --	1-10
X	JP, A, 61118289 (KANZAKI PAPER) 5 June 1986, see the whole document --	1-10
X	JP, A, 6054883 (FUJI PHOTO FILM) 29 March 1985, see the whole document	1-10

FURTHER INFORMATION CONTINUED FROM THE SECOND SHEET

V. [X] OBSERVATIONS WHERE CERTAIN CLAIMS WERE FOUND UNSEARCHABLE [1]

This International search report has not been established in respect of certain claims under Article 17(2) (a) for the following reasons:

1. [X] Claim numbers 11, because they relate to subject matter not required to be searched by this Authority, namely:

See PCT Rule 39.1(iv)
Methods for treatment of the human or animal body by surgery or therapy, as well as diagnostic methods.

2. [X] Claim numbers **, because they relate to parts of the International application that do not comply with the prescribed requirements to such an extent that no meaningful International search can be carried out, specifically:

** Claim numbers 1,7-9:
The complexity of claims 1-7 and 9, invoving a multitude of cascading meanings for the different symbols and a proviso (page 33, lines 3-6) which is incomprehensible, do not comply with article 6PCT: the scope of the sought protection is neither clearly nor concisely defined ./.

3. [ ] Claim numbers....., because they are dependent claims and are not drafted in accordance with the second and third sentences of PCT Rule 6.4(a).

VI. [ ] OBSERVATIONS WHERE UNITY OF INVENTION IS LACKING [2]

This International Searching Authority found multiple inventions in this international application as follows:

*

1. [ ] As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims of the International application.

2. [ ] As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims of the International application for which fees were paid, specifically claims:

3. [ ] No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claim numbers:

4. [ ] As all searchable claims could be searched without effort justifying an additional fee, the International Searching Authority did not invite payment of any additional fee.

Remark on Protest

[ ] The additional search fees were accompanied by applicant's protest.

[ ] No protest accompanied the payment of additional search fees.

FURTHER INFORMATION CONTINUED FROM PCT/ISA/210 (supplemental sheet (2))

Furthermore, some of the meanings of the symbols R2 in claim 3 and R1 in claim 4 are not covered by claim 1. The description does not provide any clarification for the scope of the claims, but on the contrary rather adds to the confusion by lengthy and irrelevant considerations (see for instance page 1 line 8 to page 3 line 30 and page 8 lines 7-22).
For all these reasons, the search has been limited to those compounds described in the examples or in the pharmaceutical test and/or claimed in claims 8 or 10.

ANNEX TO THE INTERNATIONAL SEARCH REPORT ON INTERNATIONAL PATENT APPLICATION NO. US 8903492 SA 30863

This annex lists the patent family members relating to the patent documents cited in the above-mentioned international search report. The members are as contained in the European Patent Office EDP file on 12/12/89
The European Patent Office is in no way liable for these particulars which are merely given for the purpose of information.

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
EP-A- 0146348	26-06-85	JP-A- 60156633	16-08-85
		US-A- 4737519	12-04-88
EP-A- 0165810	27-12-85	AU-A- 4377585	02-01-86
		JP-A- 61017579	25-01-86
EP-A- 0201071	12-11-86	US-A- 4833164	23-05-89
		JP-A- 61263943	21-11-86
		AU-A- 5718686	04-12-86
JP-A-61118289	05-06-86	None	
JP-A- 6054883	29-03-85	None	